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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,937	10/23/2003	Ping Zhou	AM100184-D1	6306

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WYETH
PATENT LAW GROUP
FIVE GIRALDA FARMS
MADISON, NJ 07940

EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,937	ZHOU ET AL.	
	Examiner	Art Unit	
	Evelyn Huang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 are pending.

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 5, 7, 8, 16, 18, and claims 1, 2, 4, 6, 9-15, 19, 20 in part, drawn to a compound of formula I wherein n=1, i.e. a 6-membered nitrogen containing ring, classified in class 546, subclass various dependent of the species elected.

II. Claim 3, and claims 1, 2, 4, 6, 9-15, 19, 20 in part, drawn to a compound of formula I wherein n=2, i.e. a 7-membered nitrogen containing ring, classified in class 544, subclass various dependent on the species elected.

These inventions are structurally distinct and have acquired a separate status in the art as shown by their different classification. A reference anticipating the 6-membered piperidinyl of group I would not render obvious the 7-membered azepinyl compound of group II. The search is therefore not co-extensive and is burdensome. Since the search required for one group is not required for the other group, restriction for examination purposes as indicated is proper.

3. During a telephone conversation with Ms. Lences on 5-20-2004 a provisional election was made with traverse to prosecute the invention of Group I, claims Claims 5, 7, 8, 16, 18, and claims 1, 2, 4, 6, 9-15, 19, 20 in part. Affirmation of this election must be made by applicant in replying to this Office action. Claims of Group II invention are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

During the telephone interview on 5-20-2004, Ms. Lences informed the examiner that in the amended claim 1, the structural formula (IVa) should have structural formula I as in the original claim 1 and currently amended claims 10, 15. The claims therefore would be examined according to the structural formula I of the original claim 1 and currently amended claims 10, 15.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 19, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The 1-(4-nitrophenyl)-, 1-(4-fluorophenyl)- or the 1-(3, 4-methoxyphenyl)- 3-(piperidin-4-yl)-1H-indazole (second, third, and fourth compound in claims 9, 19) have no antecedent basis in the base claims 1, 15 respectively wherein R5 has to be linked to Q and not directly linked to the indazolyl nitrogen as recited in the above compounds.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The method of treating a disorder of the CNS related or affected by the 5-HT6

receptor reaches out to as yet unidentified conditions/activities/disorders, the description of which is not found in the specification.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-8, 10-17, 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. *Nature of the invention.*

The instant invention is drawn to a heterocyclylindazole and azaindazole compound and its method of treating a disorder of the central nervous system related to or affected by the 5-HT6 receptor in a patient.

b. *State of the prior art and the level of the skill in the art.*

The 5-HT-6 receptor has only been recently identified using molecular biological techniques without prior knowledge of its physiological function or pharmacology. At present, there are no known fully selective agonists, as admitted by the applicant (page 4 linese 32-3). Selective antagonists for the receptor using classical medicinal chemistry have only been recently identified. The only in vivo study is with one of the antagonists, RO 04-6790, which gave rise to a behavioral syndrome of yawning, stretching and chewing; however, only the stretching behavior reached statistical significance (Sleight, PTO-1449, page1217, 1223). While 5-HT6 receptors may be implicated in the pathophysiology of several disorders, the exact roles have not been established. The conditions requiring stimulation and those requiring inhibitions have not been delineated since conclusive experimental evidence for many of the proposed function is still lacking. Furthermore, the instant compound, does not resemble these known antagonist

compounds. A compound within the scope of the instant claims has been shown to be an agonist of $5HT_{1D}$ (Slassi, WO 98/23587, PTO-1449, see paragraph 4 below).

The level of the skill in the 5-HT receptor ligand art is high.

c. *Predictability/unpredictability of the art.*

The high degree of unpredictability is well recognized in the 5-HT receptor liagnd art. A slight change in the structure of the compound would drastically alter its selectivity and affinity for the receptor, as evidenced in the different EC50 values of the structurally similar 5-HT ligand compounds (Slassi, page 50, Table).

d. *Amount of guidance/working examples.*

Preparation of example compounds has been described. The procedure for the 5-HT6 receptor binding assay is found on pages 33-34 and the result is shown for the example compounds on pages 35-36. These binding data, however, are no indication of whether the compound is an antagonist or an agonist of the receptor, nor the physiological effect upon its binding to the receptor. The specification is silent as to whether the inventive compounds are agonists or antagonists. No in vivo procedures are described.

e. *The breadth of the claims.*

Since the conditions associated with 5-HT6 receptor remain speculative at the time of the invention, Applicant's assertion that all the structurally diverse compounds embraced by the generic claim (including those with substituents further substituted by multiple substituents) would be effective in treating all disorders of the central nervous system related to or affected by the 5-HT6 receptor (both positively and negatively related or affected) does not commensurate with the scope of the objective enablement since the conditions associated with 5-HT6 receptor remain speculative at the time of the invention, especially in view of the high degree of unpredictability in the art (paragraphs c, d above).

f. *Quantitation of undue experimentation.*

In view of the high degree of unpredictability in the art and the fact that the breadth of the claims does not commensurate with that of the objective enablement, the disclosure as presented would not allow one of ordinary skill in the art to use the

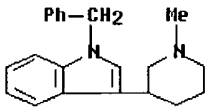
invention as claimed without undue experimentation (paragraphs b-e above). Indeed, more teaching and guidance would be required because the 5-HT6 receptor ligand art is still at its infancy stage and conclusive experimental evidence for many of the proposed function is still lacking.

Claim Rejections - 35 USC § 102

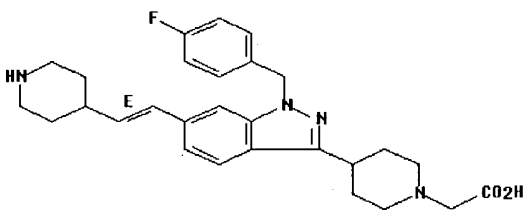
8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

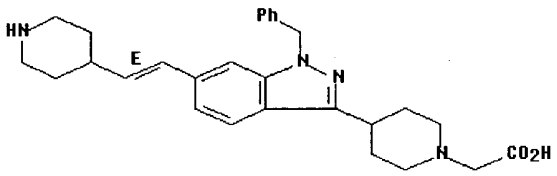
> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 2, 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Julia (Bulletin de la Societe Chimque de France (1964), 8:1939-45). The compound with the following structure is encompassed by the instant claims.

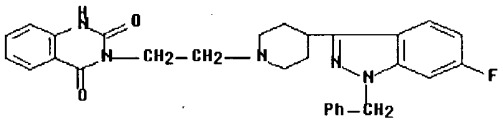


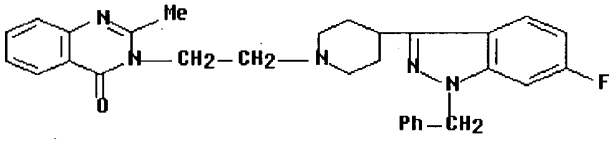
10. Claims 1, 4, 6, 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Allen I (5861414). The compounds with the following structures, and the composition thereof, are encompassed by the instant claims. The acetic acid on the piperidinyl nitrogen reads on the instant substituted alkyl of R11; the piperidinyl-ethenyl reads on the substituted alkenyl of R1 or R2.

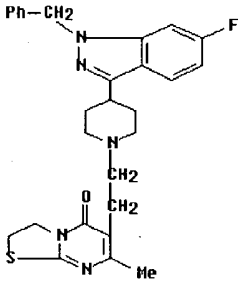




11. Claims 1, 4, 6, 10-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Vandenberk (5196425). The compounds of the following structures, the composition and method of use thereof (column 11, lines 55-68), are encompassed by the instant claims. The quinozolindione ethyl, the 4-oxo-pyrido[1,2-a]pyrimidinyl-ethyl, or the thazolo[3,2-a]pyrimidine-5-one on the piperidinyl nitrogen reads on the substituted alkyl of R11.

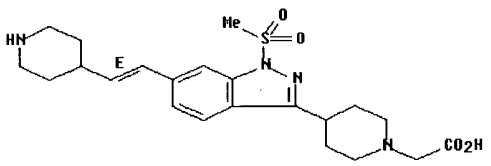


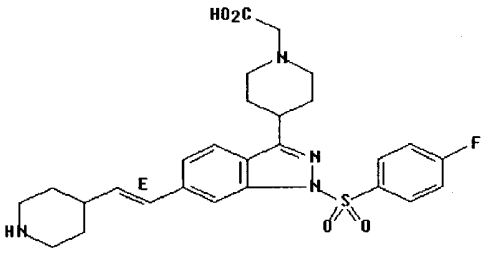




12. Claims 1, 4, 6, 15, 17, 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Allen II (WO 97/49698). The compounds of the following structures, the composition and method of use thereof (column 11, lines 55-68), are encompassed by the instant claims. The

acetic acid on the piperidinyl nitrogen reads on the instant substituted alkyl of R11; the piperidinyl-ethenyl reads on the substituted alkenyl of R1 or R2





13. Claims 1, 4, 6, 9-13, 15, 17, 19, 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Strupczewski (4670447). The compound of Example 18 (column 38), the composition and method of use thereof (column 2, lines 47-51), are encompassed by the instant claims.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5, 10-15, 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hallett (WO 99/47511).

Hallett generically discloses a 5-HT antagonizing indolyl compound for treating a CNS disorder (pages 3-4). Specific compounds, such as 3-piperidinyl-3yl- 2-phenyl-1H-indole, are described (page 9, line 7).

Hallett's example compound has a hydrogen whereas the instant has an ethyl on the indolyl nitrogen.

Hallett, however, teaches that hydrogen and alkyl such as ethyl are optional choices (page 4, line 21, definition of R3).

At the time of the invention, one of ordinary skill in the art would be motivated to replace the hydrogen with the alternative alkyl, such as ethyl, to arrive at the instant invention, with the reasonable expectation of obtaining an additional 5-HT antagonizing compound for use in the treatment of a CNS disorder.

15. Claims 1, 2, 4-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strupczewski (4670447).

Strupczewski generically discloses an indazolyl compound for treating psychosis, depression, pain etc. (columns 1-2; columns 77-78). Specific compounds are described (column 38, Example 18; column 40, Example 26; column 42, Example 33).

Strupczewski's example compound has a piperidinyl-4-yl whereas the compound of instant claims 2, 5, 7, 8, 16 has a piperidinyl-3-yl. The instant is therefore the positional isomer of the prior art compound. Furthermore, Strupczewski teaches that piperidinyl-4-yl and piperidinyl-3-yl are optional choices (column 78, lines 63-65, definitions of m and n)

At the time of the invention, one of ordinary skill in the art would be motivated to replace piperidinyl-4-yl of Strupczewski's example compound with the alternative piperidinyl-3-yl positional isomer to arrive at the instant invention, with the reasonable expectation of obtaining an additional compound useful in the treatment of psychosis, depression, or pain.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Evelyn Huang
Primary Examiner
Art Unit 1625

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